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RUTHENIUM(IV) TETRAKIS(TRIFLUOROACETATE), A NEW OXIDIZING AGENT.[1,2] III. AN EFFICIENT ACCESS TO THE APORPHINE AND HOMOAPORPHINE SKELETONS AND THEIR STRUCTURAL STUDIES.

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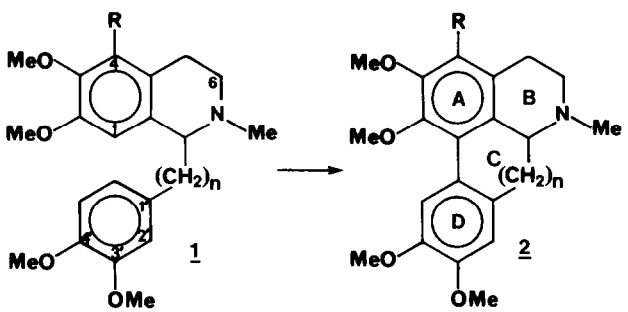
Abstract: The title reagent -RUTFA- couples efficiently phenylalkyltetrahydroisoquinolines, and the syntheses of glaucine, thalicsimidine and homoglaucine were carried out. The stereostructures of the aporphine and homoaporphine skeletons were determined by using PMR at 500 MHz.

In the course of our synthetic investigations on the synthesis of antitumor bridged biaryl lignans,[1,2] we have found that ruthenium(IV) oxide in trifluoroacetic acid medium gave better results than known reagents in non-phenol oxidative coupling of bisalkoxybenzylbutanolides.[3] The present work establishes the high interest of ruthenium(IV) tetrakis(trifluoroacetate) -RUTFA- in biomimetic syntheses of bridged biaryl alkaloids pertaining to the biologically active series of aporphines and homoaporphines from the corresponding phenylalkyltetrahydroisoquinoline precursors.

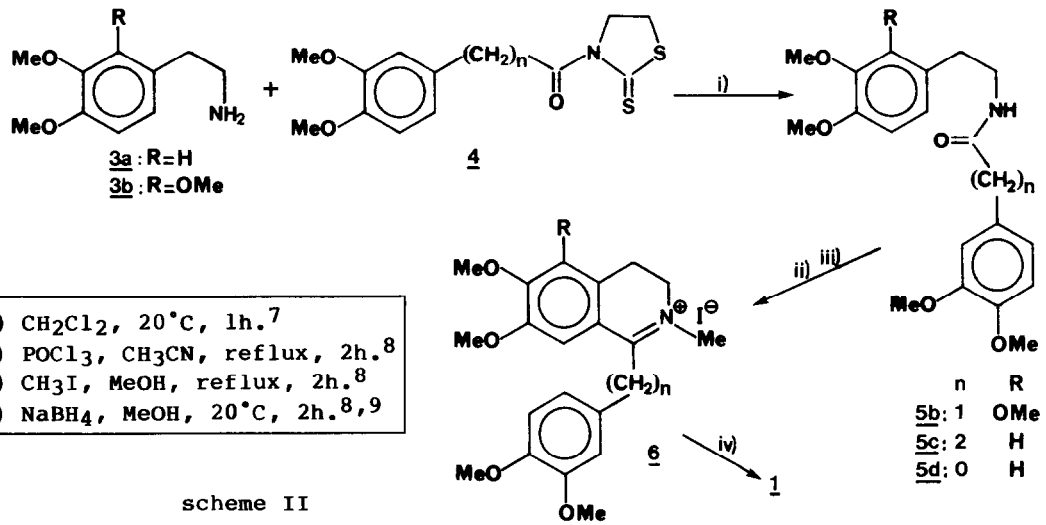


		n	R
Laudanosine	1a	1	H
Precursor	1b	1	OMe
Homolaudanosine	1c	2	H
Cryptostyline	1d	0	H
Glaucine	2a	1	H
Thalicsimidine	2b	1	OMe
Homoglaucine	2c	2	H

Scheme I

In order to compare various coupling methods, conversion of 1a, 1b and 1c into glaucine 2a, thalicsimidine 2b and homoglaucine 2c, respectively (see scheme I), was chosen as a model reaction, whereas cryptostyline 1d failed to cyclize to the corresponding indeno-[1,2,3-ij]isoquinoline in the same conditions.[4]

The suitable precursors 1b, 1c and 1d were prepared by improving known procedures.[5] The amides 5 were prepared by the reaction of N-benzoylthiazolidinethione 4[6] and the suitable amine 3 (CH_2Cl_2, 20°C, 60 min.),[7] followed by Bischler-Napieralski cyclization (see scheme II). In this manner, amides 5b, 5c and 5d were obtained in 75, 82 and 60 % yields, respectively, then where subsequently transformed into benzylisoquinoline 1b, homolaudanosine 1c and cryptostyline 1d (see scheme II) in 95, 85 and 80% yields respectively.[8,9]



i) CH_2Cl_2, 20°C, 1h.[7]
ii) $POCl_3$, CH_3CN, reflux, 2h.[8]
iii) CH_3I, MeOH, reflux, 2h.[8]
iv) $NaBH_4$, MeOH, 20°C, 2h.[8,9]

scheme II

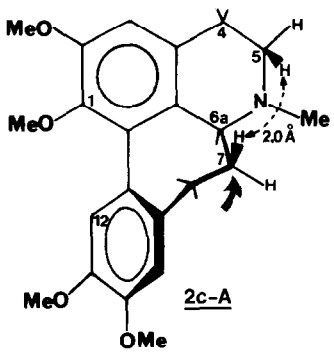
Cyclization was carried out, a) with thallium(III) tris(trifluoroacetate) -TTFA, the best reagent known yet in this case- ,[10] b) with RUTFA alone and c) by using the latter with ultrasonic assisted stirring. In all cases, metal trifluoroacetates were supposed to be generated in situ by the action of trifluoroacetic acid on the suitable oxide.[1,2] Trifluoroacetic anhydride was used as dehydrating agent and boron trifluoride etherate as electrophilic assistance agent.[10] Additionally, data on the performance of vanadium(V) oxyfluoride were collected from literature.[8,11]

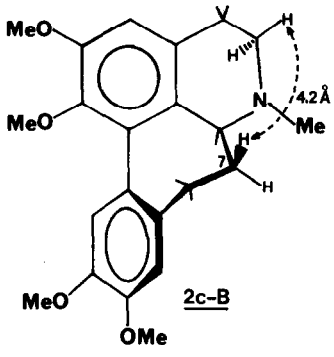
	RUTFA conditions (yield)	TTFA conditions (yield)	VOF_3[a] (yield)
2a	2 equiv,[b] 20°C, 24h (76%)	0.55 equiv, 20°C, 8h (65%)	(43%)[11]
2b	2 equiv,[b] 20°C, 16h (68%)	0.55 equiv, 20°C, 12h (57%)	
2c	2 equiv,[b] 20°C, 12h (60%)	0.55 equiv, 20°C, 1h (47%)[12]	(40%)[8]

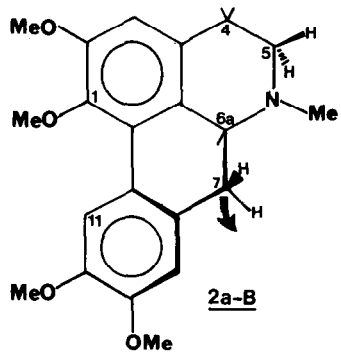
TABLE I: Reaction conditions and relative performances of oxidative coupling agents. [a]Collected from literature for VOF_3. [b]4 equiv without ultrasounds (same yields).

As shown in the above table, the best yields were obtained by using the ultrasound assisted RUTFA procedure. As previously pointed out in the case of other intramolecular biaryl couplings,[1,2] better yields than TTFA were due to the cleanliness of the final reaction medium, since, contrary to the case of TTFA, RUTFA and its reduced product were probably only poorly soluble in these conditions. Furthermore, this generally allows dispensing with chromatographic purification.

In the case of cryptostyline 1d, despite the appearance of the expected colour, characteristic of the radical cation, the starting material was recovered unchanged after 24h.[13] Thus, glaucine 2a was obtained in 76% yield, mp 134-136°C (CH_2Cl_2/ether) lit.[11] 137-139°C; thalicsimidine 2b in 68%,[14] **IR**(nujol) 3424 and 1609 cm^{-1}, **PMR** ($CDCl_3$) 2.19 to 3.21 (7H, m, aliphatic H), 2.53 (3H, s, CH_3-N), 3.70 (3H, s, OMe), 3.87 (3H, s, OMe), 3.90 (6H, s, 2 x OMe), 3.94 (3H, s, OMe), 6.74 (1H, s, H-8) 7.93 (1H, s, H-11)[15] and homoglaucine 2c in 60% yield[16] **IR** ($CHCl_3$) 1599 cm^{-1}, **PMR**[17] ($CDCl_3$) 2.56 (3H, s, CH_3-N), 3.44 (3H, s, OMe), 3.86 (3H, s, OMe), 3.90 (3H, s, OMe), 3.94 (3H, s, OMe), 6.70 (1H, s, H-3), 6.77 (1H, s, H-9) and 7.08 (1H, s, H-12), for aliphatic part, see table II.







		H-4α	H-4β	H-5α	H-5β	H-6a	H-7α	H-7β	H-8α	H-8β	H-12[a]	OMe-1
Glaucine	2a	3.12	2.67	3.02	2.45	3.03	3.01	2.57	-	-	8.09	3.65
Homoglaucine	2c	3.12	2.81	3.06	3.35	3.46	2.15[b]	2.54[b]	2.40[b]	2.45[b]	7.08	3.44

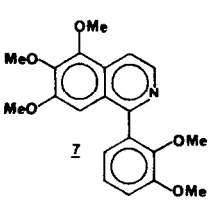
TABLE II: Comparative PMR data at 500 MHz of glaucine and homoglaucine.
[a]Numbered H-11 for 2a. [b]Exchangeable values.

Homoglaucine **2c**, which has not yet been isolated from nature, pertains to the rare class of homoaporphinic alkaloids (above represented as perspective views of the Dreiding models). The latter bear a cage-shaped stereostructure that contrasts with the quasi-planar structure of the glaucine **2a**. Due to the lack of reliable spectroscopic data, little is known about the stereostructure of homoaporphine. Large differences in the PMR data of **2a** and its homologue **2c** can be pointed out following careful comparison of the Dreiding model of the two only possible B-ring conformations of both these compounds, in connection with their high resolution PMR spectra. Thus, the ortho-biaryl proton (H-11) of **2a**, at 8.09 ppm, is high-field shifted up to 7.08 ppm for the same proton (H-12) of homoglaucine **2c**. Secondly, due to the anisotropic effect of the opposite aromatic nucleus,[18a] ortho-methoxyl on C-1 is more high-field shifted (0.2 ppm). In fact, **2a** bears aromatic PMR features of the dihydrophenanthrenic skeleton, while **2c** exhibits typical data of the original bisbenzocycloheptadiene skeleton.[18b] As indicated in table II, among the four protons H-4α , H-4β , H-5α and H-5β , the latter proton alone exhibits an unexpected large down-field shift (0.9 ppm) for **2c** and the first three have similar coupling patterns and positions. As recently described in a PMR based conformational study of deuteroglaucine,[19] the above represented conformer of **2a** predominates in solution. On manipulating the Dreiding models of both the compounds, it is clear that opposite mechanical constraints are exerted on the C-6a:C-7 bond of **2a** and **2c**, which it consecutively induces opposite conformations of their B-ring, that is to say H-5β becomes axial for the latter, and H-5β equatorial for the former. On measuring the distance between H-5β and H-7β on the models of both the conformers **2c-A** and **2c-B** of homoglaucine (see figure), it is clear that the two protons are in contact for the former (distance lower than two van der Waals radii), explaining the large low-field shift of H-5β as compared with the same proton in glaucine. Thus, contrary to glaucine, it may be predicted that the **2c-A** conformer predominates in solution.[20]

Bibliography and notes

1. Part I, Y. Landais and J.P. Robin, Tetrahedron Letters, 27, 1785 (1986).
2. Part II, Y. Landais, A. Lebrun, and J.P. Robin, Tetrahedron Letters, 27, 5377 (1986).
3. Including thallium(III) tris-trifluoroacetate and vanadium(V) oxyhalides.
4. As recently found by McKillop et al. on related examples, A. McKillop, H.N.L. Davies,

and E.C. Taylor, Synthetic Communication, 16 (3), 267 (1986).
5. Laudanosine **1a** comes from commercial source.
6. Generated from the corresponding acids and mercaptothiazoline (DMAP-DCC/MeCN, 25°C, 12 h); E. Brown, R. Joyeau, and M. Paterne, Tetrahedron Letters, 30, 2575 (1977).
7. Y. Nagao, K. Seno, and K. Kawabata, Tetrahedron Letters, 21, 841 (1980).
8. S.M. Kupchan, O.P. Dhinga, and C.K. Kim, V. Kameswaran, J. Org.Chem., 43, 2521 (1978).
9. T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, J. Chem. Soc. (C), 1032 (1971).
10. E.C. Taylor, J.G. Andrade, G.J.H. Rall, and A. McKillop, J. Am. Chem. Soc., 102, 6513, (1980).
11. S.M. Kupchan, V. Kameswaran, A. J. Liepa, and R.F. Bryan, J. Am. Chem. Soc., 95, 6861 (1973).
12. Homolaudanosine had been recently synthesized in only 21% yield by using separately prepared TTFA; F.R. Hewgill and M.C. Pass, Aust. J. Chem, 38, 555 (1985). A natural analogue of the later (O-methylkreysigine) had been prepared in 46% yield (TTFA).[10]
13. It was assumed that this failure was due to the too long minimal distance between C-1 and C-2'. In order to overcome this difficulty the planar phenylisoquinoleine **7** was synthesized in the following manner:



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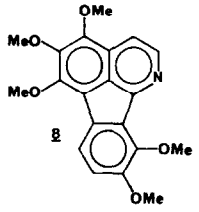

8

Amide **5a** (n = 0, R = OMe) was prepared from **3b** and 2,3-dimethoxybenzoyl chloride (quantit.), and submitted to the Bischler-Napieralsky cyclization then aromatized (Pd/C, p-cymene, reflux) to give phenylisoquinoleine **7** in 66% overall yield, mp 104-105 °C. Unfortunately, as for cryptostyline, **7** failed to give the azafluoranthene skeleton **8**, pertaining to the Abuta and Telitoxicum alkaloids series; M.P. Cava, K.T. Buck, and A.I. DaRocha, J. Amer. Chem. Soc., 94, 5931 (1972).
14. Characterized as perchlorate mp 232-235°C (MeOH-ether) lit.[9] 220-225°C.
15. Z.F. Ismailov, M.V. Jelezhenetskaya, and S. Yunusov, Khim. Prirod. Soedinenii, 4, 136 (1968).
16. Characterized as chlorhydrate mp 239-242 °C (MeOH-ether) lit.[8] 242-244°C.
17. Complete proton assignment was achieved by using selective decoupling experiments at 500 MHz. By irradiating H-4β, benzylic coupling was observed on aromatic proton H-3 (0.3 Hz).
18. a) A. Brossi, J.C. Brien, and S. Teitel, Helv. Chim. Acta, 52 , 678 (1969); b) equally found in the bisbenzocyclooctadiene lignans series; M. Taafrout, F. Rouessac, and J.P. Robin, Tetrahedron letters, 24, 197 (1983).
19. K.M. Kerr, A.M. Kook, and P.J. Davis, J. Nat. Prod, 49, 576 (1986).
20. Additionally, due to the interdependence of the two chirality centres (C-6a and biaryl), homoglaucine exists as only one racemic. Complete structural studies of this series will be published elsewhere.

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